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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,454	03/22/2005	Augustinus Bader	LORWER P33AUS	7961

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DAVIS & BUJOLD, P.L.L.C.
FOURTH FLOOR
500 N. COMMERCIAL STREET
MANCHESTER, NH 03101-1151

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 02/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/523,454	BADER, AUGUSTINUS	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-60* is/are pending in the application.

4a) Of the above claim(s) *38-40,45 and 50-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-37,41-44 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I (claims 31-49) in the reply filed on 5 December 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 50-60 are hereby withdrawn as being directed to non-elected inventions.

In response to the species election requirements applicants elected "hydrogel" (from claim 37) as the material of the boundary layer, and "lipid layer" (from claim 44) as the material of the intermediate layer; claims 38, 39, 40, and 45 are hereby withdrawn as being directed to non-elected species.

Status of Application

Claims 31-37, 41-44, and 46-49 have been examined for patentability. Claims 31-60 remain pending in the current application, of which 38-41, 45, and 50-60 have been withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-37, 41-44, and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 31 is directed to a method for culturing cells, comprising the steps of: introducing the cells into a cell culture chamber which is formed in an interior of a support structure, the cells forming a cell layer, the support structure at least approximately corresponding in shape and in size

to one of an implant and a prosthesis to be formed by the cells; supplying at least one of nutrients and oxygen to the support structure; and externally furnishing the support structure with a boundary layer which is impermeable to the cells.

Applicant's claim 31 is confusing in that it is directed to multiple statutory classes of invention in a single claim. Claim 31 can be interpreted to be directed to a method of making a cell culture system comprising (method of making), the cell culture system itself (product), or a method of using the cell culture system to culture cells (method of using); because claim 31 can be interpreted to be directed to multiple statutory classes of invention, it is unclear which single invention is intended to be claimed. The claim can be interpreted to be directed to method of making a cell culture system because the method includes steps of assembling the cell culture substrate and providing cells to the substrate; additionally, dependent claims are directed to methods of further modifying the structure of the cell culture substrate. Alternatively, though the preamble states a method for culturing cells, the body of the claim fails to recite any particular cell culture steps, rather the claim limitations, both in the independent and dependent claims, are directed to different modifications of the cell culture system itself; therefore the claims could alternatively be interpreted as being directed to the cell culture system, per se (product). Finally, because the preamble states "a method for culturing cells," one could interpret the claimed method to be directed to a method of culturing cells, wherein the limitations concerning the physical cell culture system are only considered as far as they affect the method of culturing the cells. While the claim is ambiguous and indefinite, in order to provide compact prosecution the claims will be interpreted as a method of culturing cells, as suggested by the preamble, and examination on the claimed method of culturing cells has been conducted as such. Only those limitations directed to the culturing of cells have been read into the claims.

Therefore, applicant's claim 31 is interpreted as a method for culturing cells, comprising:

(a) introducing cells into a cell culture chamber in the interior of a support structure where the cells form a cell layer; and

(b) supplying at least one of nutrients or oxygen to the support structure;

wherein the support structure at least approximately corresponding in shape and in size to an implant or prosthesis to be formed by the cells; and

wherein the support structure is externally furnished with a boundary layer which is impermeable to cells.

Please note, under the present interpretation, 'externally furnishing the support structure with a boundary layer' is not considered a step in the claimed method of cell culture; therefore it is only considered as far as it limits the method of cell culture.

It is unclear in claim 31, as interpreted above, if there should be a separate step of allowing the cells to form a cell layer. Claim 31 is further unclear regarding how the support structure corresponds in shape and in size to an implant or prosthesis to be formed by the cells, the method does not provide for forming an implant or prosthesis, but only for culturing cells.

Furthermore, it is unclear if the cell culture chamber is a separate, single compartment, surrounded by the support structure, such that the cell culture chamber is epicentric to the support structure; or if the 'cell culture chamber' is not a single space, but rather consists of a network of spaces defined by pores in a porous support structure, such that the cells are dispersed within the support structure and thereby the support structure is both the cell culture chamber and the support structure.

Still further, it is unclear in what is meant by "approximately corresponding in shape and size to an implant or prosthesis;" 'approximately corresponding' is a relative term which renders the claim indefinite. The term "approximately corresponding" is not defined in the claim, nor does the specification provide a standard for ascertaining the requisite degree of 'correspondence' between the cell culture and implants or prostheses, therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore the claim is rendered indefinite because one skilled in the art cannot determine the metes and bounds of the claimed subject matter.

Still further, it is unclear what applicant means by "externally furnishing" the support structure with a boundary layer. It is not clear if the support structure must be completely coated ('externally furnished') with a boundary layer, or if only a portion of the support structure must be 'externally furnished' with a boundary layer. It appears that a plate or dish would serve the function of the boundary layer, wherein a support structure resides in the plate or dish, the plate or dish would 'externally furnish' at least a portion of the support structure.

The dependent claims will be interpreted as far as they limit the method of cell culture:

Claim 32 is interpreted as "The method according to claim 31, wherein the support structure comprises a porous material which is permeable to cells."

Claim 33 is interpreted as "The method according to claim 31, wherein the support structure comprises a place holder material which is removable or convertible by the cells." It is unclear what is considered a "place holder material;" furthermore, it is unclear how cells remove such place holding material, while cells are capable of degrading different materials, they do not remove it, per se, nor is it clear what the place holder is converted into.

Claim 34 is interpreted as "The method according to claim 33, wherein the support structure comprises phosphate."

Claim 35 is interpreted as "The method according to claim 32, wherein the cells and a nutrient solution are introduced to the support structure prior to application of a boundary layer." Claim 35 is indefinite because parent claim 31 already requires the cells and a nutrient solution to be introduced to the support structure via the cell culture chamber. Furthermore, under the present interpretation there is no step of applying a boundary layer; therefore, this step renders the claim indefinite.

Claim 36 is interpreted as "The method according to claim 31, wherein the boundary layer comprises a biological material or a synthetic material."

Claim 37 is interpreted as "The method according to claim 36, wherein the boundary layer comprises a hydrogel."

Claim 41 is interpreted as "The method according to claim 31, wherein the boundary layer is gas permeable."

Claim 42 is interpreted as "The method according to claim 31, wherein the boundary layer is applied by spraying on a material which is impermeable to the cells or by dipping in a bath." Because the method of cell culture does not comprise an active step of applying a boundary layer, claim 42 is only considered as far as it limits the method of cell culture by the presence of a boundary layer; the method of producing the boundary layer is considered part of the method of making the cell culture system, a separate statutory class of invention not presently examined.

Claim 43 is interpreted as "The method according to claim 31, wherein an intermediate layer which does not bond to the support structure is present between the support structure and the boundary layer."

Claim 44 is interpreted as "The method according to claim 43, wherein the intermediate layer comprises a lipid layer." It is unclear how a lipid layer would form in the presence of aqueous culture medium, for in aqueous medium lipids would be expected to spontaneously form small micelles. Therefore, it is not clear how applicant creates a lipid layer, that is not bound to the support substrate, between the support substrate and the boundary layer. The metes and bounds of such a claim cannot be determined by one of ordinary skill in the art.

Claim 46 is interpreted as "The method according to claim 31, wherein the support structure comprises at least one inlet for at least one of oxygen and nutrients."

Claim 47 is interpreted as "The method according to claim 31, wherein the boundary layer is mechanically removable."

Claim 48 is interpreted as "The method of claim 31, wherein the boundary layer is detachable or soluble and is vascularized or prevascularized." It is not clear which of these characteristics are required in the boundary layer, as the options are not clearly presented in alternative forms. Additionally, it is not clear what is considered "prevascularized." Still further, it is not clear what the boundary layer consists of that would cause it to be vascularized, or how such vasculogenesis is induced. It is not clear if a separate step is required to induce vasculogenesis or to maintain vasculogenesis within the cell culture.

Claim 49 is interpreted as "The method according to claim 31, further comprising step (c) introducing a plurality of the support structures into a nutrient solution." It is not clear how this additional step corresponds with the method of claim 31; it is not clear why or when the support structures are to be introduced into a nutrient medium, i.e. before introducing cells, after introducing cells, after formation of a cell layer, etc. Furthermore, it is unclear if the plurality of support structures are to somehow be associated with one another; if the plurality of support structures are not associated with one another, it would appear the step only requires multiple cell cultures to be carried out simultaneously.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-36, 41-43, 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Bader (WO 01/09282, as translated for US national stage application 10/048,440).

Applicant's claim 31 is directed to a method for culturing cells, comprising: (a) introducing cells into a cell culture chamber in the interior of a support structure where the cells form a cell layer; and (b) supplying at least one of nutrients or oxygen to the support structure; wherein the cells culture chamber is

formed in an interior of a support structure; wherein the support structure at least approximately corresponding in shape and in size to an implant or prosthesis to be formed by the cells; and wherein the support structure is externally furnished with a boundary layer which is impermeable to cells. Claim 32 requires the support structure to comprise a porous material which is permeable to cells. Claim 33 requires the support structure to comprise a place holder material which is removable or convertible by the cells. Claim 34 requires the support structure to comprise phosphate. Claim 35 requires the cells and a nutrient solution to be introduced to the support structure prior to application of a boundary layer. Claim 36 requires the boundary layer to comprise a biological material or a synthetic material. Claim 41 requires the boundary layer to be gas permeable. Claim 43 requires an intermediate layer which does not bond to the support structure to be present between the support structure and the boundary layer. Claim 46 requires the support structure to comprise at least one inlet for at least one of oxygen and nutrients. Claim 47 requires the boundary layer to be mechanically removable. Claim 48 requires the boundary layer to be detachable or soluble and to be vascularized or prevascularized.

Bader teaches a cell culturing device and a method of culturing cells on said device. The cell culture device of Bader comprises a support, such as a cell carrier plate; a carrier film laid directly on the support; and a flexible plastic cell-culture film that is attached at the edges to the carrier plate and/or carrier film so as to form a cell culture chamber between the two films (See Bader, abstract). The cells may be cultured in the cell culture chamber directly on the films or an extracellular matrix may be placed in the interior of the cell culture chamber to provide a substrate for the cells (See Bader, Pg. 11, ln 7-19).

The extracellular matrix functions as the support structure. The matrix can approximate the size and shape of a desired tissue, for example, bone, heart valve or bladder, so that the finished cell culture may be used to reconstruct the desired tissue (See Bader, Pg. 14, ln 9-17). Specifically Bader teach the matrix can comprise collagen (See Bader, Pg. 14, ln 26-36) or tricalcium phosphate (See Bader, Pg. 11,

ln 14-19), both porous materials which are permeable to the cells and which can be degraded or absorbed (which applicant calls removable or convertible) by the cells (Claims 32-34).

The films act as the boundary layer, surrounding ("externally furnishing") the extracellular matrix (support structure). The cell carrier and/or cell culture films (boundary layer) may be gas-permeable (See Bader, abstract) (Claim 41); because the films form the cell culture chamber, both films (boundary layer) must be impermeable to cells so as to retain the cell culture in the defined area. Bader teaches the films (boundary layers) may consist of PTFE, silicone, polylactide, polyhydroxyalkanoate, or polyhydroxidebutyrates (See Bader, Pg. 18, ln 24-30); such materials are synthetically made from biological materials, thus they are considered both 'synthetic' and 'biological' materials (Claim 36). The films (boundary layers) may be removable or dissolvable after culturing is completed (See Bader, Pg. 14, ln 14-21) (Claims 47 and 48). Though the films are not applied by spraying on a material or dipping in a bath, the method of application of the films (boundary layers) does not effect the claimed method of cell culture; therefore the films (boundary layers) are one and the same as those required in the presently claimed method despite their method of application (Claim 42).

Bader teach culturing the cells by introducing cells into the matrix (support structure) in the cell culture chamber (formed by the films (boundary layers)) and supplying nutrients to the matrix (support structure) via inflow and outflow lines, and supplying oxygen to the matrix (support structure) through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27) (Claim 31 & 46). The nutrient media which fills the cell culture chamber surrounds the matrix (support structure) and functions as an intermediate layer between the support structure and the boundary layer (Claim 43). Alternatively, the cells can be introduced into the matrix externally from the cell culture chamber, and then the cell-imbibed matrix can then be injected into the cell culture chamber (formed by the films (boundary layers)), which applicant calls introducing the cells into the support structure prior to

application of the boundary layer (See Bader, Pg. 16, ln 27-30) (Claim 35). Therefore the reference anticipates the claimed subject matter.

Claims 31-32, 35-36, 42, 46, and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleinman (Current Protocols in Cell Biology, 1998).

Applicant's claim 31 is directed to a method for culturing cells, comprising: (a) introducing cells into a cell culture chamber in the interior of a support structure where the cells form a cell layer; and (b) supplying at least one of nutrients or oxygen to the support structure; wherein the cells culture chamber is formed in an interior of a support structure; wherein the support structure at least approximately corresponding in shape and in size to an implant or prosthesis to be formed by the cells; and wherein the support structure is externally furnished with a boundary layer which is impermeable to cells. Claim 32 requires the support structure to comprise a porous material which is permeable to cells. Claim 35 requires the cells and a nutrient solution to be introduced to the support structure prior to application of a boundary layer. Claim 36 requires the boundary layer to comprise a biological material or a synthetic material. Claim 42 requires the boundary layer to be applied by spraying on a material which is impermeable to the cells or by dipping in a bath. Claim 46 requires the support structure to comprise at least one inlet for at least one of oxygen and nutrients. Claim 49 requires a further step (c) introducing a plurality of the support structures into a nutrient solution.

Kleinman teaches a method for preparing gelled substrates and methods of culturing cells on the gelled substrates. Kleinman teaches means for coating tissue culture plates with liquid collagen or Matrigel solutions, and allowing the solutions to gels. Kleinman then teaches cells can be cultured on the gelled substrates by introducing cells and medium to the coated culture dish and incubating the dish in appropriate conditions (See Kleinman, Pg. 10.3.2 & 10.3.4). Alternatively, to embed the cells within the

Matrigel substrate, liquefied Matrigel can be added to cells and then the Matrigel-cell solution can be introduced to the tissue culture plates (See Kleinman, pg. 10.3.4).

The gelled substrates (either collagen or Matrigel) are considered to the support structure, the plastic tissue culture plate is considered to be the boundary layer which is impermeable to cells; therefore, Kleinman teaches a method of culturing cells by introducing cells into a gelled substrate (support structure) and supplying culture medium and oxygen to the support structure through an inlet (physical opening of culture dish), wherein the support structure is externally furnished with a tissue culture dish (boundary layer) (Claims 31 & 46). Alternatively, when the cells are mixed with Matrigel prior to being introduced to the tissue culture plates, the method effectively involves introducing the cells to the support structure prior to application of the boundary layer (See Kleinman, Pg. 10.3.4) (Claim 35). Collagen and Matrigel are naturally porous and permeable to cells (Claim 32). Standard plastic tissue culture dishes are made of synthetic materials (Claim 36). Though the tissue culture plate (boundary layer) is not applied by spraying on a material or dipping in a bath, the method of application of the tissue culture plate (boundary layer) does not effect the claimed method of cell culture; therefore the tissue culture plate (boundary layer) are one and the same as those required in the presently claimed method despite their method of application (Claim 42). Finally, in the protocols Kleinman refers to multiple tissue culture dishes, therefore it appears multiple tissue culture dishes are to be coated and used for culture simultaneously; therefore the method of Kleinman involves introduction of culture medium to a plurality of support structures contained in the tissue culture plates (Claim 49). Therefore the reference anticipates the claimed subject matter.

Claims 31, 35-37 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Schinstine et al (US Patent 5,858,747).

Applicant's claim 31 is directed to a method for culturing cells, comprising: (a) introducing cells into a cell culture chamber in the interior of a support structure where the cells form a cell layer; and (b) supplying at least one of nutrients or oxygen to the support structure; wherein the cells culture chamber is formed in an interior of a support structure; wherein the support structure at least approximately corresponding in shape and in size to an implant or prosthesis to be formed by the cells; and wherein the support structure is externally furnished with a boundary layer which is impermeable to cells. Claim 35 requires the cells and a nutrient solution to be introduced to the support structure prior to application of a boundary layer. Claim 36 requires the boundary layer to comprise a biological material or a synthetic material. Claim 37 requires the boundary layer to comprise a hydrogel. Claim 42 requires the boundary layer to be applied by spraying on a material which is impermeable to the cells or by dipping in a bath.

Schinstine et al teach a method of preparing a bioartificial organ comprising culturing cells on CultiSphers encapsulated in a cell-impermeable alginate-calcium chloride membrane (which applicant calls a hydrogel) (See Schinistine et al, col. 32, ln 59- col. 33, ln 7).

Schinstine et al teach introducing the cells into collagen-coated CultiSphers, which function as the support structures; the cell-coated CultiSphers are then suspended in an alginate matrix and immersed in a calcium chloride solution to cross-link the alginate to form cell-impermeable alginate-calcium chloride membranes (biological materials), which applicant calls boundary layers (Claims 35-37). The cells/CultiSphers/matrix were then loaded into the bioartificial organ and were supplied with appropriate medium conditions for cell culture (Claim 31). Though the method by which the boundary layer membrane is formed does not effect the claimed method of cell culture, Schinistine et al do teach immersing the cell-coated CultiSphers in alginate and then in calcium chloride solutions, this is considered to read on applicant's claim of 'dipping in a bath' (Claim 42). Therefore the reference anticipates the claimed subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651